Remarks/Arguments

Amendments to the Claims

Claims 1-3, 5-8, 10-12 and 15 have been amended. Claims 16-22 and 24-25 have been withdrawn. Claim 4 has been cancelled.

Election/Restrictions

Applicants would like to thank the Examiner for revising the restriction requirement and rejoining Groups I-VII. The Examiner has maintained the restriction between Groups I and VIII. Applicants again traverse. While it is true that Group VIII requires an additional step of screening compounds, the fact that an additional step is articulated does not justify restriction. Indeed, the claims include the same technical feature defined by Claim 1 and, thereby, possess unity of invention. In fact the inventions of the two claims could be viewed as being a combination (Group VIII) and subcombination (Group I). Restriction between these classes of invention require two way distinctness. Because the combination (Claim 16) as claimed cannot be practiced without utilizing the subcombination as claimed (Claim 1), the Examiner simply cannot establish two way distinctness. As such, restriction is improper. See PCT Administrative Instructions Annex B(c)(i) and MPEP 806.05(c).

Specification

The Examiner objects to the abstract because the PCT abstract is used and is not on a separate sheet. The specification has been amended to include the abstract on a separate sheet.

The specification was also objected to because of typographical errors on page 10, line 16 and page 40, line 16. The specification has been amended to correct these typographical errors.

The Examiner also requested that Applicants check the specification for additional typographical errors and make appropriate amendments. As requested by the Examiner, the specification has been amended to correct additional typographical errors.

Rejection under 35 U.S.C § 101

Claim 1 was rejected under 35 USC 101 as allegedly directed to non-statutory subject matter. The Examiner argues that the claimed method reads on the natural biosynthesis of heparin sulfate.

Claim 1 has been amended to recite an "in vitro method for the production of a library of heparan sulfate derivatives." The claim as amended does not read on the natural biosynthesis of heparin sulfate.

Withdrawal of this rejection is therefore respectfully requested.

Rejection under 35 U.S.C § 112

Claims 1-15 and 23 are rejected under 35 USC 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner asserts that claim 1 is indefinite for failing to recite positive process steps by which the library has been made, that claim 3 is indefinite for "non-sequitur" for the term "heparin sulfate starting material," and that claim 15 is indefinite for the use of parenthetical statements.

Claim 1 has been amended to recite the step of "chemically modifying a heparan sulfate starting material" wherein at least three of said chemical modifications are selected from A to O. The claim as amended recites a positive process step.

Claim 3 was rejected as lacking antecedent basis for the term "heparan sulfate starting material." As discussed above, claim 1 has been amended to recite the chemical modification of a heparan sulfate starting material. As amended, there is antecedent basis for the term "heparan sulfate starting material" in claim 3.

Claim 15 has been amended to delete the parenthetical statement. Furthermore, the claim has been amended to clarify which steps may be conducted together. As amended, the claim is not indefinite.

For the reasons stated above, withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C § 102

A. 102(a) rejection in view of Wu et al.

Claims 1-15 are rejected under 35 USC 102(a) as allegedly being anticipated by Wu et al. The Examiner argues that Wu et al. discloses a method of making a heparin sulfate derivative prepared by 3-O and 6-O sulfation of completely de-sulfated and N-resulfated heparin sulfate (Office Action, page 9). The Examiner additionally argues that the 3-O and 6-O sulfations are most important for AT-III binding and the Wu et al method therefore reads on claim 15. The Examiner asserts that the method taught by Wu et al. could be used to identify critical functional groups on heparin sulfate and to generate a library. The Examiner concludes that claims 1 and 15 are anticipated by the specific process steps of Wu et al. using specific combinations of desulfation and re-sulfation and creating a further library from the first library, respectively.

Claim 1 has been amended to require three process steps selected from the steps A to O and to require that at least one chemical modification be partial, thereby achieving a library of molecules (as compared to a singular product). Wu et al. does not disclose the method of the claims as amended. First, Wu et al. does not disclose three process steps selected from A to O. Wu et al. starts its method with a completely de-sulfated and N-resulfated heparin sulfate which is subjected to 3-O and/or 6-O sulfation. Second, Wu et al. does not disclose a method of modifying heparin sulfate wherein at least one method is partial. Therefore, Wu et al. does not disclose the method of preparing a heparin sulfate library comprising three process steps selected from the step A to O wherein at least one chemical modification is partial.

Withdrawal of this rejection is therefore respectfully requested.

B. 102(b) rejection in view of Ben-Artzi (U.S. Pat. No. 6,190,875)

Claims 1-15 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Ben-Artzi et al. The Examiner quotes sections of the Ben-Artzi patent and states that the quoted sections read on claims 1 and 15 (Office Action, page 10).

As discussed above, the claims have been amended to require three process steps selected from the steps A to O wherein at least one chemical modification is partial. Ben-Artizi et al. does not disclose a method of preparing a library wherein at least one

chemical modification step is partial. Each of the steps described Example 1 of Ben-Artizi et al. are complete modifications including "complete N-desulfation," "total desulfation of N and O sulfate groups" and "O-desulfated, N-acetylated heparin." Ben-Artizi et al. therefore does not anticipate the claims as amended.

C. 102(b) rejection in view of Kariya et al. or Baumann et al. or Ungarelli et al.

Claims 1-15 and 23 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Kariya et al., Baumann et al. or Ungarelli et al. With regard to Kariya et al. and Baumann et al., the Examiner contends that each of the references teach methods of making libraries of heparin sulfate derivatives where the library contains "at least two of the modifications" of claim 1. The Examiner additionally argues that the two references disclose the method of claim 15. With respect to Ungarelli et al., the Examiner contends that the reference teaches a method of producing a library having a disclosed structural formula which encompasses a heparin sulfate derivative having the "claimed modifications of e.g., sulfation, de-sulfation and so on" (Office Action, page 12).

The claims as amended require three process steps selected from A to O wherein at least one chemical modification is partial. Neither Kariya et al. nor Baumann et al. disclose three chemical modification steps. Kariya et al. discloses two chemical modification steps: solvolysis and N-resulfation. Baumann et al. also discloses the same two modification steps: solvolysis and N-resulfation. Therefore, neither Kariya et al. nor Baumann et al. anticipates the claims as amended.

Ungarelli et al. is directed to a method of producing a heparin derivative having the structural formula III wherein the 2-position of α-L-iduronic acid is substituted with a nucleophilic group having the formula ZR_1R_2 where Z is oxygen, sulfur or nitrogen and R_1 is straight or branched alkyl, amino, aryl, diazo or hydroxyl (Column 7, lines 1-54). Ungarelli et al. discloses that the process starts with a glycosaminoglycan of formula I. Ungarelli et al. discloses that the advantage of the disclosed process is obtaining "the product of formula III in only one reaction by starting from the glycosaminoglycan of formula I instead obtaining it by means of two consecutive reactions…" (Column 3, lines 58+). The chemical reaction described in Ungarelli et al. involves reacting a compound of formula I with a nucleophilic reagent in the presence of an inorganic or organic base

(Column 8, lines 25+). In contrast, the present invention is directed to a method of preparing a library of heparin derivative wherein three chemical modification steps are selected from the steps A to O. Ungarelli et al. does not disclose a method of preparing a library comprising three chemical modification steps selected from the steps A to O. As such, Ungarelli et al. does not anticipate the claimed method.

D. 102(b) rejection in view of den Born, Maccarana et al. or Petitou et al.

Claims 1-15 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by den Born, Maccarena et al. or Petitou et al. The Examiner states that each of these references discloses a method of making a library by modifying heparin sulfate comprising "desulfation, resulfation and O-desulfation, partial or complete" (Office Action, page 13).

den Born et al. discloses the preparation of de-aminated glycosaminoglycans, N-acetylated glycosaminoglycans, N-deacetylated glycosaminoglycans, N-desulfated glycosaminoglycans, completely (N- and O-) desulfated, N-deacetylated heparin and N-deacetylated O-sulfated heparin, (p 31304 and 31306-7). N-sulfated oligosaccharides were prepared by deacetylating GlcNAc residues using hydrazinolysis followed by deamination. N-acetylated oligosaccharides were prepared by deaminating the polysaccharide at acidic pH. N-acetylated GlcN was prepared by acetylation. den Born et al. teach that completely (N- and O-) desulfated, N-deacetylated heparin was prepared by deacetylation and complete (N- and O-) desulfation using HCl in methanol followed by hydrolysis under basic conditions (see Jacobsson et al. (1979) and Kantor et al. (1957)). den Born et al. therefore does not disclose a method comprising three chemical modification steps selected from the steps A to O wherein at least one step is partial. At most, den Born et al. teaches two chemical modifications steps which are each complete. den Born et al. therefore does not anticipate the claims as amended.

Maccarana et al. disclose the preparation 6-O-desulfated heparin was obtained using de-sulfation followed by re-N-sulfation. Maccarena et al. disclose that heparin was 6-O-desulfated "along with" N-desulfation (p23898). Maccarena et al. disclose that "one third of the 2-O-sulfate groups must have been lost along with the 6-O-sulfates."

Maccarena et al. therefore disclose two chemical modification steps and does anticipate the present claims.

Petitou et al. disclose the preparation of heparin derivatives by the introduction of sulfate groups on the iduronic acid and glucosamine units (p637). Petitou et al. disclose the preparation of seven heparin derivatives shown in FIG. 1 (p638). Petitou et al. does not disclose the preparation of a library of heparin sulfate derivatives using three chemical modification steps wherein at least one modification is partial. As such, Petitou et al.does not anticipate the claims as amended.

Rejection under 35 U.S.C 103(a)

Claims 1-15 and 23 are rejected under 35 USC 103(a) as being unpatentable over any one of Ben-Artzi et al., Wu et al., den Born et al., Maccarana et al., and Petitou et al. (the primary references) in view of Kariya et al. The Examiner states that the primary references do not teach complete de-N-sulfation in glucosamine. The Examiner alleges that Kariya et al. teaches N-desulfation by solvolysis. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use the N-desulfation step to prepare a library of heparin derivatives.

As discussed above, the claims have been amended to require three steps selected from A to O wherein at least one chemical modification is partial. Each of the references cited by the Examiner disclose chemical modification of a heparin sulfate starting material but none of the references teaches the specific combination of steps required by the present claims. Specifically, none of the primary references discloses the three steps selected from A to O, wherein at least one chemical modification is partial. The teaching of Kariya et al. does not remedy this deficiency. Kariya et al. discloses only two chemical modification steps. There is no teaching in the primary references or in Kariya et al. that would render the presently claimed method obvious.

Withdrawal of this rejection is therefore respectfully requested.

Conclusion

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to

issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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